Posttranscriptional control of the stem cell and neurogenic programs by the nonsense-mediated RNA decay pathway.

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Public Summary:
Stem cells can both proliferate and differentiate. The mechanisms dictating this decision are poorly understood. Here, we report that a protein that has the ability to bind to RNA--UPF1--plays a key role in this decision by promoting the proliferative, undifferentiated cell state. UPF1 acts by stimulating the decay of messenger RNAs encoding key proteins that drive differentiation. Differentiation of neural stem cells is triggered when NMD is downregulated by a small RNAs that are ~22 nucleotides long called microRNAs. The specific microRNAs that silence NMD are induced by neural differentiation signals. This UPF1-microRNA circuit is present not only in mammals but also frogs, indicating it is an ancient and highly conserved pathway that controls stem cell proliferation vs. differentiation decisions.

Scientific Abstract:
The mechanisms dictating whether a cell proliferates or differentiates have undergone intense scrutiny, but they remain poorly understood. Here, we report that UPF1, a central component in the nonsense-mediated RNA decay (NMD) pathway, plays a key role in this decision by promoting the proliferative, undifferentiated cell state. UPF1 acts, in part, by destabilizing the NMD substrate encoding the TGF-beta inhibitor SMAD7 and stimulating TGF-beta signaling. UPF1 also promotes the decay of mRNAs encoding many other proteins that oppose the proliferative, undifferentiated cell state. Neural differentiation is triggered when NMD is downregulated by neurally expressed microRNAs (miRNAs). This UPF1-miRNA circuitry is highly conserved and harbors negative feedback loops that act as a molecular switch. Our results suggest that the NMD pathway collaborates with the TGF-beta signaling pathway to lock in the stem-like state, a cellular state that is stably reversed when neural differentiation signals that induce NMD-repressive miRNAs are received.